REMARKS

Reconsideration and withdrawal of the rejections of the claimed invention is respectfully requested in view of the amendments, remarks and enclosures herewith, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1-23 are pending in this application. Support for the amendment to claim 1 can be found, e.g., in paragraph [0013] of the publication of this application. New claims 21-23 are more directly targeted to the product QUTENZA®, which is further explained in section III. below, and have been added to provide alternative positions for Appeal should the broader claims not be held to be allowable. No new matter has been added by this amendment.

The applicants appreciate the Examiner according time to the applicants' representative to discuss the merits of the case during the interview of 8 December 2009. The applicants have reviewed the Interview Summary Form and are in agreement with the description in the "Substance of the Interview" section.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited in the Office Action, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112.

II. THE 35 U.S.C. 112, 1st PARAGRAPH REJECTION HAS BEEN OVERCOME

Claims 1-20 were rejected as allegedly lacking adequate written description. The applicants request reconsideration of this rejection for the following reasons.

The claims were rejected for the applicants' use of terms "capsaicin analog". However, this term is not only part of the applicants' specification, but also the originally filed claims. It is well known that there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) ("we are of the opinion that the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims"); *See also* MPEP 2163, section II. A.

Moreover, the Office Action cited U.S. Patent 6,239,180 ("Robbins '180") in the obviousness and obviousness-type double patenting rejections which are addressed in greater detail in sections III. and IV. below.

Robbins '180 and Robbins (U.S. Patent 6,248,788) are both described in the applicants' background section of the specification (see paragraph [0002] of the publication of this application). Robbins '180 not only refers to "capsaicin analogs" throughout their specification, but it is also part of their claims (see e.g. claims 1 and 3). As such, one of ordinary skill in the capsaicin arts is apprised of the meaning and scope of the term capsaicin analog and would have presumed that the applicants and Robbins had possession of the concept of capsaicin analog absent any evidence to the contrary.

Lastly, the applicants note that maintaining this rejection is an implicit rejection of the allowed claims of Robbins '180. However, each claim of a patent is presumed to be valid. *See* 35 U.S.C. 282. As such, maintaining this rejection is casting aspersions on a previously issued U.S. patent which is explicitly not permitted. MPEP 1701 - Office Personnel Not to Express Opinion on Validity or Patentability of Patent.

III. THE 35 U.S.C. 103(a) REJECTION HAS BEEN OVERCOME

Claims 1-20 were rejected as allegedly being obvious by Müller (WO 01/01967) in view of Robbins (US 6,239,180 – "Robbins") and Schacht et al. (US 2005-0079206 -"Schacht"). The applicants request reconsideration of this rejection for the following reasons.

WO 01/01967 is the publication of the PCT application which resulted in U.S. Application Serial No. 10/835,997 ("the '997 application"), which is subject to the obviousness-type double patenting rejection addressed in section IV. below. Dr. Walter Müller is the named inventor in both WO 01/01967 and the present application.

A. Allowability of species inventions over the genus invention

During the 8 December 2009 interview between the Examiner and the applicants' representative (Howard C. Lee), it appeared a general agreement was reached that this application represented a "species" invention in relation to the "genus" represented by the '997 application, i.e. whereas both application are directed toward the use of microreservoirs with amphiphilic solvents, the present application is specifically directed toward capsaicin and capsaicin analogs instead of being generically directed to therapeutic compounds.

It was also noted during the interview that the applicants have already received a "species" patent wherein the therapeutic compound was fentanyl (see U.S. Patent 7,390,500 – "the '500 patent"). As such, the applicants were confused by the nature of the rejection for this application (as well as the genus application) as the rejection appears to be revisiting old issues which have already been decided, i.e. the Examiner in the '500 patent also considered WO 01/01967 and the fentanyl claims in the '500 patent were allowed.

B. No rationale for combining WO 01/01967 with Robbins and Schacht

In order to establish a prima facie case of obviousness, both the applicants' claimed invention and the cited references must be considered as a whole. While this does not preclude the use of any part of the cited reference, the overall teaching of the reference must be considered as well.

The Office Action stated that it would have been obvious to "…replace the analgesic agent with capsaicin or capsaicin analog taught by Robbins." (see page 10, lines 6-7 of the Office Action). WO 01/01967 is generic for therapeutic compounds, but Robbins does not provide the requisite teaching or suggestion to combine capsaicin or capsaicin analog into the applicants' topical patch not only for the reason of unexpected results which is described below in section C., but because Robbins is directed toward a fundamentally different invention.

Robbins clearly requires an anesthetic in combination with their invention which is not a required element of the present invention. ("Transdermal application of capsaicin (or a capsaicin analog) in a concentration from greater than about 5% to about 10% by weight has been discovered to be an extremely effective therapy for treating neuropathic pain, ***so long as an anesthetic***, preferably by means of a transdermal patch, is administered initially to the affected area to minimize the expected side effect from subsequent capsaicin application." - see Abstract of Robbins (emphasis added))

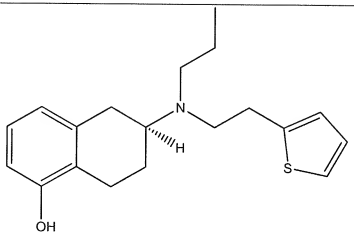
Moreover, Robbins cannot even contemplate that high concentrations of capsaicin is even possible without an anesthetic ("Because the patient in the following example describes long term pain relief much beyond the expected duration of the regional anesthetic, this relief cannot be due to the action of the anesthetic alone and is due to the combination of the block and capsaicin (***since administration of the high concentration capsaicin without the anesthetic would not be possible***)." – see col. 4, lines 45-52 (emphasis added)).

Therefore, Robbins does not suggest the replacing of capsaicin as the therapeutic compound, but a combination of capsaicin ***and*** an anesthetic as the therapeutic compound, i.e. even if one of ordinary skill in the art was limited to considering only the substitution of a single compound with another compound, such a selection would present an virtually an infinite number of possible solution to the problem of delivery of an analgesic.

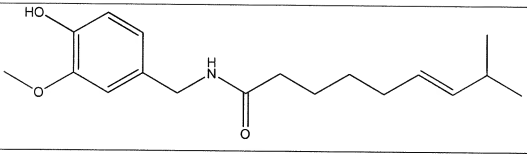
However, if Robbins is considered to be relevant art, the selection by the skilled artisan would be for an even greater number of possible solutions, i.e. multiple compound combinations would then have to be considered as is suggested by Robbins as well as single compound substitutions and if multiple compound combinations are contemplated, no evidence has been presented as to why such combinations should be limited to just the two components as in Robbins (why not 3, 4, 5…100 or more?).

The Office Action also stated that it would have been obvious to "…provide [a] transdermal patch comprising polysiloxane matrix containing microreservoirs comprising capsaicin or its analogs dissolved in an amphiphilic solvent as taught by the combined teaching of Muller and Robbins, and replace the polysiloxane matrix with a matrix comprising mixture of high tack polysiloxane and medium tack polysiloxane as taught by Schacht." (see page 10, lines 14-19 of the Office Action).

However, when considering Schacht as a whole, it is clear that Schacht is specifically directed toward addressing the difficulties associated with rotigotine which is structurally and functionally different than capsaicin (see figures and functions below):



Rotigotine
(psychoactive drug for treatment of Parkinson's disease)



Capsaicin
(topical analgesic)

Schacht makes no assertions about other therapeutic compounds besides rotigotine. The teaching of Schacht attempted to address the problem associated with rotigotine with regard to keeping the compound in free base form, i.e. minimizing the amount of salt form, and keeping the rotigotine solubilized (hence, the suggested use of crystallization inhibitors) which is not a problem in the present invention because the capsaicin is dissolved in the microreservoir.

As such, one of ordinary skill in the art would not have been directed to taking the isolated element of a mixture of high tack polysiloxane and medium tack polysiloxane as taught by Schacht for use of a rotigotine delivery system into a topical patch for capsaicin or a capsaicin analog. Moreover, there is even some doubt that Schacht is even effective for their own teachings (see entry for rotigotine in Wikipedia attached to the end of this response – "As of 2008, Schwarz Pharma has recalled all Neupro (rotigotine) patches in the United States and some in Europe because of problems with the delivery mechanism.").

Therefore, when considering WO 01/01967, Robbins and Schacht as a whole, there is no direction to piece the disparate parts relied upon to arrive at the applicants' claimed topical patch which is directed to capsaicin and capsaicin analogs.

C. Combination of WO 01/01967, Robbins and Schacht does not suggest that capsaicin/microreservoir system would have a permeation rate which is double that of a system without microreservoirs

Determinations of obviousness also requires consideration of any evidence of secondary considerations. Here, the applicants have shown that a topical patch of the invention has a permeation rate which is twice that of a topical patch which does not have a microreservoir system. Neither Robbins not Schacht would have predicted this unexpected permeation rate for capsaicin in the claimed topical patch.

Likewise, whereas WO 01/01967 is generic for therapeutic compounds and could encompass capsaicin, there is no suggestion that capsaicin should be selected as a preferred analgesic because of the unexpected permeation rates as has been shown by the applicants.

D. Note about FDA approved product within the scope of pending claims

Although the purpose and function of the USPTO and the FDA are different, the applicants note for the record that the product QUTENZA® has been approved for sale in the U.S. and that QUTENZA® has been designated with ***Orphan Drug*** status for the treatment of neuropathic pain associated with postherpetic neuralgia.[1] (see attachments – "Highlights of Prescribing Information" and article from Medical News Today dated 3 June 2009)

Whereas a patented product is normally delayed for sale in the U.S. because of the lengthy FDA approval process, we have the highly unusual situation whereby the FDA approval for the product has been granted before the patent covering the product. Given this backdrop and the recent changes to RCE practice which can favor an Appeal Brief over a RCE to receive an expedited final decision on the claims, the applicants encourage the Examiner to contact the undersigned if an Examiner's Amendment is necessary to place the application in condition for allowance.

IV. THE OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION HAS BEEN OVERCOME

Claims 1-20 have been provisionally rejected under obviousness-type double patenting over claims 32-55 of co-pending Application No: 10/835,997 in view of Robbins (US 6,239,180 -"Robbins"). While the secondary reference used to support this reject has changed from Holt (US 6,348,501) to Robbins, the main argument previously presented by the applicants still applies, i.e. while there are certain similarities between the analysis for an obviousness rejection and an obviousness-type double patenting (ODP) rejection, the rejections are not the same, i.e. the analysis for an ODP rejection is limited to a comparison of the respective claims and does not allow for the use of secondary references except for explanatory purposes (e.g. defining the meaning of a claim term). *See MPEP 804.*

[1] The U.S. Orphan Drug Act was intended to encourage development of products which demonstrate promise for the diagnosis, prevention and/or treatment of rare diseases and conditions affecting 200,000 patients of less.

However, in the present case, Robbins is being used to address a missing element of the applicants' claim. Therefore, the use of the Robbins is *prima facie* evidence that a basis for ODP does not exist and this rejection should be withdrawn. Moreover, even if Robbins had been an appropriate reference for use, Robbins was specifically directed to capsaicin and capsaicin analogs; it is not instructive of selecting capsaicin and capsaicin analogs from a generic teaching of a therapeutic compound or was predictive of the fact that the permeation rate of capsaicin and capsaicin analogs could be doubled by the use of microreservoirs of amphiphilic solvent in the matrix of the topical patch.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution. The Commission is authorized to charge any fee occasioned by this paper, or credit any overpayment of such fees, to Deposit Account No. 50-0320.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

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Rotigotine

See original Wikipedia article »

From Wikipedia

This page was last modified on 10 February 2010, at 05:26.

Rotigotine (**Neupro**) is a non-ergoline dopamine agonist psychoactive drug and is indicated for the treatment of Parkinson's disease (PD). It was developed by Dr. Gevork Minaskanian, cofounder of Aderis Pharmaceuticals. In 1998, Aderis licensed worldwide development and commercialization rights for rotigotine to the German pharmaceutical company Schwarz Pharma (today a subsidiary of the Belgian company UCB S.A.). Rotigotine is intended to be delivered through transdermal patches, so as to ensure a slow and constant dosage in a 24-hour period

The drug has been approved by the EMEA for use in the EU in 2006 and is today being sold in several European countries. In 2007, the Neupro patch was approved by the Food and Drug Administration (FDA) as the first transdermal treatment of Parkinson's disease in the United States. In their press release, the FDA mentioned the following side effects (among others): "skin reactions at the patch site, dizziness, nausea, vomiting, drowsiness and insomnia... are typical of this drug class."

As of 2006, the phase III clinical trial results showed that the drug was able to significantly reduce off time and increase on time without troublesome dyskinesia.

As of 2008, Schwarz Pharma has recalled all Neupro patches in the United States and some in Europe because of problems with the delivery mechanism.

References

External links

Rotigotine™ (SPM-962) - The First Once-a-Day Transdermal Patch to Treat Parkinson's Disease
Reuters - US FDA approves Parkinson's Patch
Developer's webpage
Manufacturer's webpage
Website [1] for Neupro
BBC News article: Skin patch hope for Parkinson's
Medscape article: Transdermal Rotigotine Patch Safe, Effective in Early Idiopathic Parkinson's Disease
Bandolier article: Rotigotine for restless legs syndrome - concludes that there is insufficient evidence for the use of rotigotine for treating RLS
Owner's webpage for Neupro

Rotigotine

Systematic (IUPAC) name

(*S*)-6-[propyl[2-(thiophen-2-ylethyl)amino]-5,6,7,8-tetrahydronaphthalen-1-ol

Identifiers	
CAS number	92206-54-7
ATC code	N04BC09
PubChem	57937
Chemical data	
Formula	$C_{19}H_{25}NOS$
Mol. mass	315.474 g/mol
Pharmacokinetic data	
Bioavailability	37% (transdermal)
Protein binding	92%
Metabolism	Hepatic (CYP-mediated)
Half life	5 to 7 hours
Excretion	Renal (71%) and fecal (23%)
Therapeutic considerations	
Licence data	EU EMEA link
Pregnancy cat.	?
Legal status	POM (UK)
Routes	Transdermal patch

Antiparkinson Agents (N04) [show]

Dopaminergics [show]

Retrieved from "http://mediawiki.fr.dp.teoma.com/wiki/Rotigotine"
Categories: Dopamine agonists | Thiophenes

Related Questions

What is rotigotine
Rotigotine has some of the same effects as a chemical called dopamine, which occurs naturally in your body. Low levels of dopamine in the brain are associated with Parkinson's disease. Rotigotine is u...

How To Use Rotigotine TD
This medicine comes with a Patient Information Leaflet. Read it carefully. Ask your doctor, nurse, or pharmacist any questions that you may have. Follow the package instructions for using this medicat...

How much does rotigotine cost
The cost rating is based on the average wholesale price for a drug. The average wholesale price is the suggested selling price for a drug, much like the sticker price on a car. Insurance companies oft...

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Related Images

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use QUTENZA safely and effectively. See full prescribing information for QUTENZA.

QUTENZA® (capsaicin) 8% patch
Initial U.S. Approval: 2009

----------INDICATIONS AND USAGE----------
- Qutenza is a TRPV1 channel agonist indicated for the management of neuropathic pain associated with postherpetic neuralgia (PHN). (1)

----------DOSAGE AND ADMINISTRATION----------
- Only physicians or health care professionals under the close supervision of a physician are to administer Qutenza. (2.1)
- Do not use Qutenza on broken skin. (2.1)
- Apply Qutenza to the most painful skin areas, using up to four patches. (2.2)
- Apply Qutenza for 60 minutes and repeat every 3 months or as warranted by the return of pain (not more frequently than every three months). (2.2)
- Use only nitrile (not latex) gloves when handling Qutenza and when cleaning treatment areas. (2.1)
- Before patch application, a physician must identify and mark the painful area, including areas of hypersensitivity and allodynia. (2.2)
- Apply a topical anesthetic before Qutenza application. (2.3)
- Apply Qutenza by placing on the skin while slowly removing the release liner from underneath. (2.3)
- Remove the Qutenza patches by gently and slowly rolling them inward. (2.3)
- After removal of Qutenza, apply Cleansing Gel for one minute and then remove it with a dry wipe. (2.3)
- Treat acute pain during and following the procedure with local cooling and/or analgesics. (5.4)
- Dispose of patches and other treatment materials immediately after use in accordance with local biomedical waste procedures. (2.1)
- The treated area may be sensitive for a few days to heat (e.g., hot showers/baths, direct sunlight, vigorous exercise). (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
- Qutenza patch contains 8% capsaicin (640 mcg/cm^2). Each patch contains a total of 179 mg of capsaicin. (3)

----------CONTRAINDICATIONS----------
- None

----------WARNINGS AND PRECAUTIONS----------
- Do not use near eyes or mucous membranes. (5.1)
- Inhalation of airborne capsaicin can result in coughing or sneezing. (5.2)
- If irritation of eyes or airway occurs, remove the affected individual from the vicinity of Qutenza and flush the mucous membranes or eyes with water. If skin not intended to be treated comes into contact with Qutenza, apply Cleansing Gel and then wipe off with dry gauze. (5.2, 5.3)
- Transient increases in blood pressure may occur in patients during and shortly after the Qutenza treatment. Monitor blood pressure during and following the treatment procedure. For those patients who require the use of opioids to treat pain during or following the procedure, their ability to perform potentially hazardous activities such as driving or operating machinery may be affected. (5.4, 5.5)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥ 5% and greater than control) are application site erythema, application site pain, application site pruritus and application site papules. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact NeurogesX at 1-877-900-NGSX (6479) or FDA at 1-800-FDA-1088 or www.fda.gov/medwateh.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: November 2009

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Qutenza is indicated for the management of neuropathic pain associated with postherpetic neuralgia.

2 DOSAGE AND ADMINISTRATION

2.1 Special Precautions

- Only physicians or health care professionals under the close supervision of a physician are to administer Qutenza.
- Use only nitrile gloves when handling Qutenza, and when cleaning capsaicin residue from the skin. Do not use latex gloves as they do not provide adequate protection.
- Immediately after use, dispose of used and unused patches, Cleansing Gel and other treatment materials in accordance with the local biomedical waste procedures.
- Use Qutenza only on dry, intact (unbroken) skin.
- Apply the Qutenza patch within 2 hours of opening the pouch.

2.2 Dosing

The recommended dose of Qutenza is a single, 60-minute application of up to four patches.

Treatment with Qutenza may be repeated every three months or as warranted by the return of pain (not more frequently than every three months).

2.3 Instructions for Use

Prepare

Put on nitrile gloves. Inspect the pouch. Do not use if the pouch has been torn or damaged.

Identify

The treatment area (painful area including areas of hypersensitivity and allodynia) must be identified by a physician and marked on the skin.

If necessary, clip hair (do not shave) in and around the identified treatment area to promote patch adherence.

Qutenza can be cut to match the size and the shape of the treatment area.

Gently wash the treatment area with mild soap and water and dry thoroughly.

Anesthetize

Pre-treat with a topical anesthetic to reduce discomfort associated with the application of Qutenza.

Apply topical anesthetic to the entire treatment area and surrounding 1 to 2 cm, and keep the local anesthetic in place until the skin is anesthetized prior to the application of Qutenza patch.

Remove the topical anesthetic with a dry wipe. Gently wash the treatment area with mild soap and water and dry thoroughly.

Apply

Tear open the pouch along the three dashed lines, remove the Qutenza patch.

Inspect the Qutenza patch and identify the outer surface backing layer with the printing on one side and the capsaicin-containing adhesive on the other side. The adhesive side of the patch is covered by a clear, unprinted, diagonally-cut release liner.

Cut Qutenza before removing the protective release liner.

The diagonal cut in the release liner is to aid in its removal. Peel a small section of the release liner back, and place the adhesive side of the patch on the treatment area.

While you slowly peel back the release liner from under the patch with one hand, use your other hand to smooth the patch down on to the skin.

Once Qutenza is applied, leave in place for 60 minutes.

To ensure Qutenza maintains contact with the treatment area, a dressing, such as rolled gauze, may be used.

Instruct the patient not to touch the patch or treatment area.

Remove

Remove Qutenza patches by gently and slowly rolling them inward.

Cleanse

After removal of Qutenza, generously apply Cleansing Gel to the treatment area and leave on for at least one minute. Remove Cleansing Gel with a dry wipe and gently wash the area with mild soap and water and dry thoroughly.

Dispose of all treatment materials as described [*see Dosage and Administration (2.1)*]

Inform the patient that the treated area may be sensitive for a few days to heat (e.g., hot showers/baths, direct sunlight, vigorous exercise)

3 DOSAGE FORMS AND STRENGTHS

Qutenza patch contains 8% capsaicin (640 mcg/cm^2). Each patch contains a total of 179 mg of capsaicin.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Eye and Mucous Membrane Exposure

Do not apply Qutenza to the face or scalp to avoid risk of exposure to the eyes or mucous membranes.

5.2 Aerosolization of Capsaicin

Aerosolization of capsaicin can occur upon rapid removal of Qutenza patches. Therefore, remove Qutenza patches gently and slowly by rolling the adhesive side inward [*see Dosage and Administration (2.3)*].

If irritation of eyes or airways occurs, remove the affected individual from the vicinity of Qutenza. Flush eyes and mucous membranes with cool water.

Inhalation of airborne capsaicin can result in coughing or sneezing. Provide supportive medical care if shortness of breath develops.

5.3 Unintended Skin Exposure

If skin not intended to be treated comes in contact with Qutenza, apply Cleansing Gel for one minute and wipe off with dry gauze. After the Cleansing Gel has been wiped off, wash the area with soap and water.

5.4 Application Associated Pain

Even following use of a local anesthetic prior to administration of Qutenza, patients may experience substantial procedural pain. Prepare to treat acute pain during and following the application procedure with local cooling (such as an ice pack) and/or appropriate analgesic medication, such as opioids. Opioids may affect the ability to perform potentially hazardous activities such as driving or operating machinery.

5.5 Increase in Blood Pressure

In clinical trials, increases in blood pressure occurred during or shortly after exposure to Qutenza. The changes averaged less than 10 mm Hg, although some patients had greater increases and these changes lasted for approximately two hours after patch removal. Increases in blood pressure were unrelated to the pretreatment blood pressure but were related to treatment-related increases in pain. Monitor blood pressure periodically during the treatment and provide adequate support for treatment related pain.

Patients with unstable or poorly controlled hypertension, a recent history of cardiovascular or cerebrovascular events may be at an increased risk of adverse cardiovascular effects. Consider these factors prior to initiating Qutenza treatment.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling.

Application-Associated Pain *[see Warnings and Precautions (5.4)]*

Increase in Blood Pressure *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in clinical practice.

Across all controlled and uncontrolled trials, more than 1,600 patients have received Qutenza. A total of 394 patients received more than one treatment application and 274 patients were followed for 48 weeks or longer.

In controlled clinical studies, 98% of patients completed ≥ 90% of the intended patch application duration. Among patients treated with Qutenza, 1% discontinued prematurely due to an adverse event.

Controlled Clinical Studies

Common Adverse Reactions

Adverse reactions occurring in ≥ 5% of patients in the Qutenza group and at an incidence greater than in the control group were application site erythema, application site pain, application site pruritus and application site papules.

Table 1 summarizes all adverse reactions, regardless of causality, occurring in ≥ 1% of patients with postherpetic neuralgia in the Qutenza group for which the incidence was greater than in the control group. The majority of application site reactions were transient and self-limited. Transient increases in pain were commonly observed on the day of treatment in patients treated with Qutenza. Pain increases occurring during patch application usually began to resolve after patch removal. On average, pain scores returned to baseline by the end of the treatment day and then remained at or below baseline levels. A majority of Qutenza-treated patients in clinical studies had adverse reactions with a maximum intensity of "mild" or "moderate".

TABLE 1:
Treatment-emergent adverse reaction incidence (%) in controlled trials in Postherpetic Neuralgia (Events in ≥ 1% of Qutenza-treated patients and at least 1% greater in the Qutenza group than in the Control group)

Body System Preferred Term	Qutenza 60 minutes (N = 622) %	Control 60 minutes (N = 495) %
General Disorders and Administration Site Conditions		
Application Site Erythema	63	54
Application Site Pain	42	21
Application Site Pruritus	6	4
Application Site Papules	6	3
Application Site Edema	4	1
Application Site Swelling	2	1
Application Site Dryness	2	1
Infections and Infestations		
Nasopharyngitis	4	2
Bronchitis	2	1
Sinusitis	3	1
Gastrointestinal Disorders		
Nausea	5	2
Vomiting	3	1
Skin and Subcutaneous Tissue Disorder		
Pruritus	2	< 1
Vascular Disorders		
Hypertension	2	1

TABLE 1: (cont.)
Treatment-emergent adverse reaction incidence (%) in controlled trials in Postherpetic Neuralgia (Events in ≥ 1% of Qutenza-treated patients and at least 1% greater in the Qutenza group than in the Control group)

Other Adverse Reactions Observed During the Clinical Studies of Qutenza

General Disorders and Administration Site Conditions: Application site urticaria, Application site paresthesia, Application site dermatitis, Application site hyperesthesia, Application site excoriation, Application site warmth, Application site anesthesia, Application site bruising, Application site inflammation, Application site exfoliation, Peripheral edema

Nervous System Disorders: Headache, Burning sensation, Peripheral sensory neuropathy, Dizziness, Dysgeusia, Hyperesthesia, Hypoesthesia

Respiratory, Thoracic and Mediastinal Disorders: Cough, Throat irritation

Skin and Subcutaneous Tissue Disorders: Abnormal skin odor

7 DRUG INTERACTIONS

No clinical drug interaction studies have been performed.

Data from *in vitro* cytochrome P450 inhibition and induction studies show that capsaicin does not inhibit or induce liver cytochrome P450 enzymes at concentrations which far exceed those measured in blood samples. Therefore, interactions with systemic medicinal products are unlikely.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category B

There are no adequate and well-controlled studies evaluating Qutenza in pregnant women.

There was no evidence of fetal teratogenicity in embryofetal developmental toxicological studies conducted in pregnant rats and rabbits in which Qutenza patches (rats) or liquid (rabbits) were applied once daily for a 3 hour duration during the period of fetal organogenesis up to doses corresponding to an 11-fold (rat, 32 mg capsaicin patch/day) and 37-fold (rabbit, 260 mg capsaicin/day) margin over the maximum recommended human dose [MRHD] based on a C_{max} exposure comparison.

In a peri- and post-natal reproduction toxicology study, pregnant female rats were treated with Qutenza patches at doses up to 32 mg

capsaicin patch/rat/day applied once daily for a 3 hours duration during gestation and lactation (from gestation day 7 through day 28 postpartum). Analyses of milk samples on day 14 of the lactation period demonstrated measurable levels of capsaicin in the dam's milk at all dose levels. There were no effects on survival, growth, learning and memory tests (passive avoidance and water maze), sexual maturation, mating, pregnancy, and fetal development in the offspring of mothers treated with capsaicin up to 32 mg capsaicin patch/rat/day (corresponding to an 11-fold margin over the MRHD based on C_{max} exposure)

8.2 Labor and Delivery

The effects of Qutenza on labor and delivery are unknown

8.3 Nursing Mothers

There are no adequate and well-controlled studies in nursing women. Studies in rat have demonstrated capsaicin is excreted into breast milk of this species. It is unknown whether capsaicin is excreted in human breast milk. Because Qutenza is administered as a single 60-minute application and capsaicin is rapidly cleared from the bloodstream [*see Clinical Pharmacology (12.3)*], mothers can reduce infant exposure by not breast-feeding after treatment on the day of treatment.

8.4 Pediatric Use

The safety and effectiveness of Qutenza in patients younger than 18 years of age have not been studied.

8.5 Geriatric Use

In controlled clinical studies of Qutenza in neuropathic pain associated with postherpetic neuralgia, 75% of patients were 65 years and older and 43% of patients were 75 years and older.

Safety and effectiveness were similar in geriatric patients and younger patients. No dose adjustments are required in geriatric patients.

10 OVERDOSAGE

There is no clinical experience with Qutenza overdose in humans.

There is no specific antidote for overdose with capsaicin. In case of suspected overdose, remove patches gently, apply Cleansing Gel for one minute, wipe off with dry gauze and gently wash the area with soap and water. Use supportive measures and treat symptoms as clinically warranted.

11 DESCRIPTION

Qutenza (capsaicin) 8% patch contains capsaicin in a localized dermal delivery system. The capsaicin in Qutenza is a synthetic equivalent of the naturally occurring compound found in chili peppers. Capsaicin is soluble in alcohol, acetone, and ethyl acetate and very slightly soluble in water.

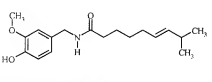
Qutenza is a single-use patch stored in a foil pouch. Each Qutenza patch is 14 cm x 20 cm (280 cm^2) and consists of a polyester backing film coated with a drug-containing silicone adhesive mixture, and covered with a removable polyester release liner.

The backing film is imprinted with "capsaicin 8%". Each Qutenza patch contains a total of 179 mg of capsaicin (8% in adhesive, 80 mg per gram of adhesive) or 640 micrograms (mcg) of capsaicin per square cm of patch.

The empirical formula is $C_{18}H_{27}NO_3$, with a molecular weight of 305.42. The chemical compound capsaicin [(E)-8-methyl-N-vanillyl-6-nonenamide] is an activating ligand for transient receptor potential vanilloid 1 receptor (TRPV1) and it has the following structure:

FIGURE 1:

Structural Formula of Capsaicin



The patch contains the following inactive ingredients: diethylene glycol monoethyl ether, dimethicone, ethyl cellulose, polyester film, silicone adhesive and white ink.

Qutenza is supplied with a Cleansing Gel which is used to remove residual capsaicin from the skin after treatment. Cleansing Gel consists of the following ingredients: butylated hydroxyanisole, carbomer copolymer, edetate disodium, polyethylene glycol, purified water, and sodium hydroxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Capsaicin is an agonist for the transient receptor potential vanilloid 1 receptor (TRPV1), which is an ion channel-receptor complex expressed on nociceptive nerve fibers in the skin. Topical administration of capsaicin causes an initial enhanced stimulation of the TRPV1-expressing cutaneous nociceptors that may be associated with painful sensations. This is followed by pain relief thought to be mediated by a reduction in TRPV1-expressing nociceptive nerve endings [*see Clinical Pharmacology (12.2)*]. Over the course of several months, there may be a gradual re-emergence of painful neuropathy thought to be due to TRPV1 nerve fiber reinnervation of the treated area.

12.2 Pharmacodynamics

Two studies evaluated the pharmacodynamic effects of Qutenza on sensory function and epidermal nerve fiber (ENF) density in healthy volunteers. Consistent with the known pharmacodynamic effects of capsaicin on TRPV1-expressing nociceptive nerve endings, reduced ENF density and minor changes in cutaneous nociceptive function (heat detection and sharp sensation) were noted one week after exposure to Qutenza. ENF density reduction and sensory changes were fully reversible.

12.3 Pharmacokinetics

Pharmacokinetic data in humans showed transient, low (< 5 ng/mL) systemic exposure to capsaicin in about one third of PHN patients following 60-minute applications of Qutenza. The highest plasma concentration of capsaicin detected was 4.6 ng/mL and occurred immediately after Qutenza removal. Most quantifiable levels were observed at the time of Qutenza removal and were below the limit of quantitation 3 to 6 hours after Qutenza removal. No detectable levels of metabolites were observed in any subject.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Adequate carcinogenicity studies have not been conducted with Qutenza or capsaicin.

Mutagenesis

Capsaicin was not mutagenic in the Ames, mouse micronucleus and chromosomal aberration in human peripheral blood lymphocytes assays. As with other catechol-containing compounds (e.g., dopamine), capsaicin showed a weak mutagenic response in the mouse lymphoma assay.

Impairment of Fertility

A fertility and reproductive toxicology study was conducted in rats with exposure to Qutenza patches daily for 3 hours/day beginning 28 days before cohabitation, through cohabitation and continuing through the day before sacrifice (approximately 49 days of treatment). The results revealed a statistically significant reduction in the number and percent of motile sperm. Sperm motility obtained from the vas deferens was reduced in all capsaicin treatment groups (16, 24 and 32 mg capsaicin patch/rat/day). Though a "no effect" level was not determined, dose levels used in the study correspond to a 13- to 28-fold exposure margin over the mean C_{max} associated with the maximal human recommended dose. Sperm counts were reduced in the vas deferens or cauda epididymis in the 24 and 32 mg capsaicin patch/rat/day dose groups (79 and 69%, respectively) compared to the placebo patch treated control group; however, these reductions did not adversely affect fertility. As this animal model has a large excess of sperm generating capacity relative to the threshold necessary for fertilization, the lack of an effect on fertility in this species is of unknown significance for human risk assessment.

14 CLINICAL STUDIES

14.1 Postherpetic Neuralgia

The efficacy of Qutenza, was established in two 12-week, double-blind, randomized, dose-controlled, multicenter studies. These studies enrolled patients with postherpetic neuralgia (PHN) persisting for at least 6 months following healing of herpes zoster rash and a baseline score of 3-9 on an 11-point Numerical Pain Rating Scale (NPRS) ranging from 0 (no pain) to 10 (worst possible pain). Qutenza and a control patch were each applied as a single 60-minute application. The control used in these studies looked similar to Qutenza but contained a low concentration of the active ingredient, capsaicin (3.2 mcg/cm^2, 0.04% w/w) to retain blinding regarding the known application site reactions of capsaicin (such as burning and erythema). The baseline mean pain scores across the 2 studies was approximately 6.0. Patients who entered the study on stable doses of pain-control medications were required to keep dosing stable throughout the duration of the study. Approximately half of the patients were taking

concomitant medications including anticonvulsants, non-SSRI antidepressants, or opioids for their PHN at study entry. Prior to study patch application a topical anesthetic was applied to the treatment area for 60 minutes. Patients were permitted to use local cooling and additional analgesic medications for treatment-related discomfort as needed through Day 5. Patients recorded their pain daily in a diary.

PHN Study 1: In this 12-week study, the Qutenza group demonstrated a greater reduction in pain compared to the Control group during the primary assessment at Week 8. The percent change in average pain from baseline to Week 8 was -18% (±2%) for the low-dose control and -29% (±2%) for Qutenza.

For various degrees of improvement in pain from baseline to study endpoint, Figure 2 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study through Week 12 or who showed no improvement at Week 12 were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study. The proportion of patients experiencing ≥ 30% reduction in pain intensity from baseline for each week through Week 12 is shown in Figure 3.

FIGURE 2:

Patients Achieving Various Percentages of Reduction in Pain Intensity at Week 12 – Study 1

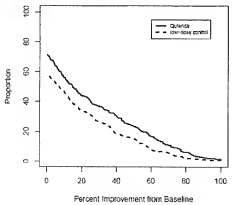
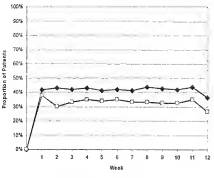


FIGURE 3:

Weekly Proportion of Patients Achieving ≥ 30% Pain Intensity Reduction – Study 1*:



*The same patients may not have responded at each timepoint.

PHN Study 2: In this 12-week study the Qutenza group demonstrated a greater reduction in pain compared to the Control group during the primary assessment at Week 8. The percent change in average pain from baseline to Week 8 was -26% (±2%) for the low-dose control and -33% (±2%) for Qutenza.

For various degrees of improvement in pain from baseline to study endpoint, Figure 4 shows the fraction of patients achieving that degree of improvement. The figure is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete the study through Week 12 or who showed no improvement at Week 12 were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout the study. The proportion of patients achieving ≥ 30% reduction in pain intensity from baseline for each week through Week 12 is shown in Figure 5.

FIGURE 4:

Patients Achieving Various Percentages of Reduction in Pain Intensity at Week 12 – Study 2

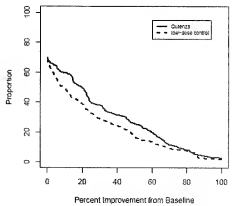
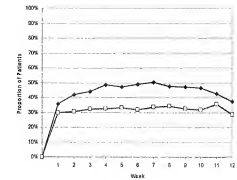


FIGURE 5:

Weekly Proportion of Patients Achieving ≥ 30% Pain Intensity Reduction – Study 2*:



*The same patients may not have responded at each timepoint.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Qutenza (capsaicin) 8% patch is a single-use patch stored in a sealed pouch (NDC 49685-920-00).

Each individual patch is printed with "capsaicin 8%".

Cleansing Gel is provided in a 50 g tube.

Qutenza is available in the following presentations:

Carton of 1 patch and 50 g tube of Cleansing Gel (NDC 49685-928-01).

Carton of 2 patches and 50 g tube of Cleansing Gel (NDC 49685-928-02).

16.2 Storage

Store carton between 20° to 25°C (68° to 77°F). Excursions between 15°C and 30°C (59°F and 86°F) are allowed.

Keep the patch in the sealed pouch until immediately before use.

16.3 Handling and Disposal

Qutenza contains capsaicin capable of producing severe irritation of eyes, skin, respiratory tract and mucous membranes. Do not dispense Qutenza to patients for self-administration. It is critical that health care professionals who administer Qutenza have completely familiarized themselves with proper dosing, handling, and disposal procedures before handling Qutenza to avoid accidental or inadvertent capsaicin exposure to themselves or others [*see Dosage and Administration (2)*].

- Do not touch Qutenza, treatment areas, and all used supplies or other materials placed in contact with the treatment area without wearing nitrile gloves.
- Wear nitrile gloves at all times while handling Qutenza and cleaning treatment areas. Do NOT use latex gloves.
- Do not hold Qutenza near eyes or mucous membranes.
- Immediately after use, dispose of used and unused patches, patch clippings, unused Cleansing Gel and associated treatment supplies in accordance with local biomedical waste procedures.

17 PATIENT COUNSELING INFORMATION

- Inform patients that exposure of the skin to Qutenza may result in transient erythema and burning sensation. Instruct patients not to touch the patch and that if they accidentally touch the Qutenza patch it may burn and/or sting.
- Instruct patients that if irritation of eyes or airways occurs, or if any of the side effects become severe, to notify their doctor immediately.
- Inform patients that the treated area may be sensitive to heat (e.g., hot showers/bath, direct sunlight, vigorous exercise) for a few days following treatment.
- Inform patients that they may be given medication to treat acute pain during and after the Qutenza application procedure. Some of these medications, such as opioids, may affect the ability to perform potentially hazardous activities such as driving or operating machinery.
- Inform patients that as a result of treatment-related increases in pain, small transient increases in blood pressure may occur during and shortly after Qutenza treatment and that blood pressure will be monitored during the treatment procedure. Instruct patients to inform the physician if they have experienced any recent cardiovascular event.
- Instruct patients to notify their physician if they are pregnant or breast feeding.

Manufactured for NeurogesX, Inc., San Mateo, CA 94404, USA
by Lohmann Therapie-Systeme AG (LTS), Andernach, Germany

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Medical News TODAY www.medicalnewstoday.com

NeurogesX Receives FDA Orphan Drug Designation For Qutenza(TM) For Treatment Of Postherpetic Neuralgia

03 Jun 2009 Click to Print

NeurogesX, Inc. (Nasdaq: NGSX), a biopharmaceutical company focused on developing and commercializing novel pain management therapies, announced that the Office of Orphan Product Development (OOPD) of the U.S. Food and Drug Administration (FDA) has granted orphan drug designation for Qutenza(TM) (formerly NGX-4010), a high concentration capsaicin dermal patch for the management of neuropathic pain in patients with postherpetic neuralgia (PHN).

The FDA is currently reviewing the Company's new drug application (NDA) for Qutenza in PHN and has assigned a Prescription Drug User Fee Act (PDUFA) date of August 16, 2009. Qutenza, if approved by the FDA, would benefit from seven years of market exclusivity in PHN as a result of this orphan designation.

The U.S. Orphan Drug Act encourages the development of products that demonstrate promise for the diagnosis, prevention and/or treatment of rare diseases and conditions affecting 200,000 patients or less. Orphan drug designation is an important economic incentive for the development of new products, providing seven years of exclusive marketing rights during which the FDA will not approve the same drug from another sponsor for the same orphan indication during the exclusivity period. In addition, orphan designation allows for reduction in certain regulatory fees, and additional regulatory support for R&D initiatives.

Anthony DiTonno, President and CEO, commented, "The FDA's orphan designation underscores the unmet need of patients suffering from PHN and may serve to strengthen Qutenza's competitive position through seven years of market exclusivity upon approval."

PHN is a chronic painful condition that develops in patients following a herpes zoster (shingles) outbreak. Current treatments for PHN include antidepressants, anticonvulsants, topical anesthetics and opioid analgesics.

About NeurogesX, Inc.

NeurogesX (Nasdaq: NGSX) is a biopharmaceutical company focused on developing and commercializing novel pain management therapies. Its initial focus is on chronic peripheral neuropathic pain, including postherpetic neuralgia (PHN), painful HIV-distal sensory polyneuropathy (HIV-DSP) and painful diabetic neuropathy (PDN). NeurogesX' late stage product portfolio is led by its product candidate Qutenza, a dermal patch designed to manage pain associated with peripheral neuropathic pain conditions. Qutenza is currently approved in the European Union for the treatment of neuropathic pain in non-diabetic adults, either alone or in combination with other medicinal products for pain. NeurogesX submitted a new drug application (NDA) for Qutenza to the U.S. Food and Drug Administration (FDA) which was accepted for filing by the FDA in December 2008 and was given a Prescription Drug User Fee Act (PDUFA) date of August 16, 2009.

NeurogesX' second most advanced product candidate, NGX-1998, is a topically applied, liquid formulation containing a high concentration of capsaicin designed to treat pain associated with neuropathic pain conditions. NGX-1998 has completed three Phase 1 studies and NeurogesX is currently evaluating the timing of entering Phase 2 development.

NeurogesX' early stage product pipeline includes pre-clinical compounds, which are prodrugs of acetaminophen and various opioids. The company has evaluated these compounds in vitro and in vivo and is currently seeking development partners for these programs.

Safe Harbor Statement

This press release contains forward-looking statements for purposes of the Private Securities Litigation Reform Act of 1995 (the "Act"). NeurogesX disclaims any intent or obligation to update these forward-looking statements, and claims the protection of the Safe Harbor for forward-looking statements contained in the Act. Examples of such statements include, but are not limited to, the extension of marketing exclusivity for Qutenza if approved by the FDA; and the timing and outcome of regulatory

decisions and label approval being sought or that may be obtained with respect to the NDA for Qutenza with the FDA. Such statements are based on management's current expectations, but actual results may differ materially due to various risks and uncertainties, including, but not limited to; positive results in clinical trials may not be sufficient to obtain FDA approval; the FDA may request additional clinical trials or other information prior to granting approval for Qutenza; any regulatory approvals which are received may be limited to certain indications; NeurogesX' product candidates may have unexpected adverse side effects or inadequate therapeutic efficacy; and other difficulties or delays in, clinical development of, and obtaining regulatory approval for NeurogesX' product candidates. For further information regarding these and other risks related to NeurogesX' business, investors should consult NeurogesX' filings with the Securities and Exchange Commission.

Source: NeurogesX, Inc

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